II. REMARKS

Preliminary Remarks:

Claim 53 is amended to more clearly identify the subject matter that is claimed.

New claims 70-80 are directed to the disclosed isolated antisense oligonucleotide that is complementary to at least a portion of a gene encoding a peripheral-type benzodiazepine receptor (PBR) that comprises the PBR amino acid sequence shown in SEQ ID NO:3; which antisense oligonucleotide inhibits the expression of said PBR gene when it is introduced into a mammalian cell that expresses said PBR gene, and thereby inhibits proliferation of said cell relative to an otherwise identical cell which does not contain said antisense oligonucleotide. New claim 75 specifies that the claimed antisense oligonucleotide is complementary to a portion of a PBR gene that encodes a fragment of a PBR protein shown in SEQ ID NO:3 that comprises the mutant residues threonine 147 and arginine 162. Support for these claims is found in the specification, for example, at page 15, line 25, to page 16, line 6. New claims 70 and 76 specify an antisense oligonucleotide that comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2. New claims 71 and 77 specify that the antisense oligonucleotide inhibits the proliferation of a human breast cancer cell containing a PBR protein that comprises the amino acid sequence shown in SEQ ID NO:3 when the oligonucleotide is introduced into said cell. New claims 72, 73, and 78-80 specify that the antisense oligonucleotide is encoded by a vector and is synthesized in a mammalian cell, *e.g.*, a human breast cancer cell, following introduction of said vector into said cell. Support for these new claims is found in the specification, for example, at page 25, line 28, to page 26, line 28.

Patentability Remarks:

Objections:

The official action objected to claim 53 for a grammatical error ("are having..."). Claim 53 has been amended to remove the error, and withdrawal of the objection is respectfully requested.

35 U.S.C. §112, First Paragraph

Claims 53-57 and 64-67 were rejected under 35 U.S.C. §112, First Paragraph, because the specification allegedly does not enable a person skilled in the art to make or use the claimed antisense oligonucleotide that inhibits expression of the disclosed cancer-associated PBR gene in a cell that expresses said PBR gene. The applicants respectfully traverse the rejection.

At the time the priority application was filed, it was well known by persons skilled in the art to which the claimed invention pertains that oligonucleotide sequences complementary to a selected gene that inhibit expression of the gene can be identified by synthesizing oligonucleotides that hybridize to overlapping target nucleotide sequences that cover a significant portion of the gene of interest, and by screening to identify the oligonucleotides that have inhibitory activity. Accordingly, while the inhibitory activity of any given oligonucleotide may be unpredictable, one of skill in the art would reasonably expect to identify one or more nucleotide sequences within the targeted gene where binding of an antisense oligonucleotide results in inhibition of the expression of the target gene.

The amended and new claims are also directed to relatively large oligonucleotides that comprise a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2, and to such oligonucleotides that are encoded by an expression vector and are synthesized in a mammalian cell following introduction of said vector into the cell. At the time the priority application was filed, methods for making and using vectors encoding large cDNAs to inhibit expression of a complementary target gene were well known in the art. Moreover, the scientific literature contains many reports showing that vector-mediated expression of a large cDNA complementary to a target gene in a mammalian cell inhibits the expression of the target gene. For example, see Ellis et al. (J Biol Chem. 1998 Jan 9;273(2):1052-7), Waki et al. (Biochem Biophys Res Commun. 1994 Jun 15;201(2):1001-7), Rutka et al. (Cancer Res. 1994 Jun 15;54(12):3267-72), and Resnicoff et al. (Cancer Immunol Immunother. 1996 Jan;42(1):64-8) (abstracts attached), to name but a few. In contrast, reports of unsuccessful attempts to inhibit the expression of the target gene in a cell by vector-mediated expression of a large cDNA complementary to a target gene are practically non-existent. In view of the numerous published reports describing inhibition of the expression of

a target gene by vector-mediated expression of an antisense cDNA, persons of skill in the art would reasonably have expected that the vector-mediated expression of a large cDNA complementary to a target PBR gene in a cell, such as a cDNA comprising SEQ ID NO:1 or SEQ ID NO:2, would similarly successfully inhibit the expression of the target PBR gene.

In view of the foregoing, the applicants submit that the specification would enable persons of skill in the art to make and use the claimed antisense oligonucleotides to inhibit expression of the disclosed mutant PBR gene without the need to perform undue experimentation. Withdrawal of the rejection of the claims under 35 U.S.C. §112, First Paragraph, is therefore respectfully requested.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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